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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/185,243	11/03/98	TSANG T	15907-0016

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/185,243	Tsang et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *May 5, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-46* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-46* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6, 7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Claims 1-46 are pending.

In view of the agreement of the examiner to rejoin Groups I-III set forth in the restriction requirement of 3/29/00, as discussed in a telephone interview on 4/27/00, and in view of applicants' arguments with respect to recombining Group IV, as set forth in applicants' response to the restriction requirement (see page 2 of applicants' Response, Paper No. 9), the restriction requirement has been withdrawn. Claims 1-46 are being examined on the merits.

Specification

The disclosure is objected to because of the following informalities: on page 67, Table 5, it is not apparent what the numbers in parentheses represent and on page 68, Table 6, it is unclear what the dashes represent.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 7, and 39-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an expression construct and method of using the expression construct wherein the expression construct comprises the heat shock promoters HSP28, HSP72

or HSP73. The specification teaches that the heat shock promoter used in generating the expression construct is optionally derived from a promoter selected from the group of the heat shock protein promoters HSP70, HSP90, HSP60, HSP27, HSP72, HSP73, HSP25, and HSP28 (see page 4, lines 13-16). While the specification specifically teaches a minimal heat shock promoter, isolated from HSP70, comprising the first approximately 400 bp of the HSP70B promoter (see page 4, lines 17-19), and while heat shock promoter elements isolated from HSP70, HSP90, HSP60, HSP27, and HSP25 have been described in the prior art (see the 35 U.S.C. 103 rejections below), the specification does not disclose the source of the promoters, nor does the specification disclose any sequence data associated with the heat shock promoters HSP28, HSP72 or HSP73. Moreover, while it is evident that cDNAs encoding hsp28, hsp72, and hsp73 proteins have been previously isolated and characterized before the time of filing of the instant invention, a search of the patent and non-patent literature databases has not revealed any references disclosing particular promoter regions of HSP28, HSP72 or HSP73.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of promoter regions of HSP28, HSP72 or HSP73, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for these promoters to be utilized in generating the claimed expression constructs.

Claims 1-15, and 17-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression construct comprising the inducible promoters, HSP70, HSP90, HSP60, HSP27, and HSP25, and ubiquitin, operably linked to a gene encoding a transactivating factor and a second promoter operably linked to a selected polynucleotide, wherein the second promoter is activated by a transactivating factor, and a method of effecting expression of a selected polynucleotide in a mammalian cell, *in vitro*, comprising introducing the expression construct into a mammalian cell, and subjecting the mammalian cell, *in vitro*, to hyperthermic conditions, does not reasonably provide enablement for

expression constructs comprising the inducible promoters, HSP28, HSP72 or HSP73 or methods of using the expression constructs comprising these promoters, a method of providing a subject with a therapeutically effective amount of an expression product of the selected polynucleotide by introducing the expression construct into a mammalian cell; a method of treating cancer in a mammal by introducing the expression construct into a mammalian cell; a method of provoking an immune response in a mammal, a method of altering the genetic material of a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 1-17 are directed to a method of effecting expression of a selected polynucleotide in a mammalian cell comprising introduction of the claimed expression construct into the cell and inducing the activation of the claimed expression construct. The claim encompasses both in vivo and in vitro methods of effecting expression in a mammalian cell.

Claims 18-26 are directed to a method of providing a subject with a therapeutically effective amount of an expression product of a selected polynucleotide comprising introduction of two constructs into the cell of the subject and inducing the activation of the constructs. The expression product can be harmful to a pathogen (claim 23), can inhibit cell growth (claim 24), can replace a deficient protein (claim 25) or can promote nerve regeneration (claim 26).

Claims 27-32 are directed to a method of treating cancer in a mammal comprising introducing an expression construct into a tumor cell and subjecting the tumor cell to conditions which induce the activation of the expression construct.

Claims 33-37 are directed to a method for provoking an immune response in a mammal comprising introducing an expression construct into a cell in the mammal and subjecting the cell to conditions which induce the activation of the expression construct.

Claim 38 is directed to a method of altering the genetic material of a mammal comprising introducing the claim-designated expression construct into a cell of said mammal.

While the specification is enabling for an expression construct comprising the inducible promoters, HSP70, HSP90, HSP60, HSP27, and HSP25, and ubiquitin, operably linked to a gene encoding a transactivating factor and a second promoter operably linked to a selected polynucleotide, and wherein the second promoter is activated by a transactivating factor, a method of introducing the expression construct into a cell, *in vitro*, and an isolated cell comprising the expression construct, the specification is not enabling for a method of treating cancer in a mammal, or a method of provoking an immune response in a mammal, a method of altering the genetic material of a mammal, or providing an expression construct comprising the inducible promoters, HSP28, HSP72 or HSP73. The specification does not provide sufficient guidance for one of skill in the art to make and use the inventions as claimed.

The specification discloses expression constructs comprising an inducible promoter operably linked to a gene encoding a transactivating factor and a second promoter operably linked to a selected polynucleotide, wherein the second promoter is activated by a transactivating factor. The specification further discloses transfecting the expression construct into two cell lines, MCF7 and Du145, and subjecting the cells to hyperthermic conditions such that the selected polynucleotide, i.e., EGFP or IL-2, is expressed (see, e.g., Examples 1-3 of the specification).

With regard to introducing the expression construct into a mammalian cell, *in vivo*, the specification broadly discloses that the expression construct can be introduced into a mammal or mammalian cell, *in vitro*, *ex vivo*, or *in vivo* (see page 54 of the specification) by viral vector- or non-viral vector-mediated transfer methods (see pages 35-47 of the specification). The specification also discloses that administration of pharmaceutical compositions comprising the expression construct can be via any common route so long as the target tissue or cell is available via that route, including oral, nasal, buccal, rectal, vaginal or topical routes; by orthotopic, intradermal, subcutaneous, intramuscular, intraperitoneal, or intravenous injection; and for the purpose of applying the pharmaceutical composition to tumors, by direct intratumoral injection, injection of a resected tumor bed, regional (e.g., lymphatic) or systemic administration, or continuous perfusion over a period of hours or days (see page 55 of the specification). The

specification indicates that an effective amount of the therapeutic agent is determined base on the intended goal, for example (I) inhibition of tumor cell proliferation, (ii) elimination or killing of tumor cells, or (iii) gene transfer for short- or long-term expression of a therapeutic gene (see page 56 of the specification). Disclosed embodiments include providing a subject with a therapeutically effective amount of a product of a selected polynucleotide, wherein the product may optionally be deleterious to a pathogen in the subject, such as a virus, bacterium, fungus, or parasite (see page 6 of the specification), where the product may inhibit the growth of a cell in a subject (see page 6 of the specification), a product which replaces a deficient protein in a subject or promotes nerve regeneration (see page 7 of the specification), or administration of a vector encoding a therapeutic gene to treat cancer patients or a viral vector encoding a therapeutic gene to vaccinate humans or other mammals (see page 57 of the specification).

While the specification broadly discloses modes of administration based on the intended goal, the specification does not provide sufficient guidance as to how one of skill in the art would specifically treat a subject suffering from nerve damage, or deficiency of an endogenously synthesized protein, cancer, a pathogen, or aberrant cell growth. There is no correlation in the specification as to a specific gene transfer method required such that administering the expression product will result in the expression of the selected therapeutic polynucleotide such that a physiological effect is obtained. The specification only provides working examples of transfecting two cell lines, *in vitro*, with expression constructs comprising a heat shock promoter, hsp70, wherein the heat shock promoter is induced in cells when the cells are subjected to hyperthermic conditions (see Examples 1-3 of the specification). It is noted that the data obtained in the experiments described in Examples 1-3 of the specification only provide data which indicates the relative inducibility of the heat shock promoter by measuring the amount of IL-2 expressed. There is no indication that the two cell lines, which can be considered tumor cell lines, are affected with respect to growth rates or display any changes which would be associated with an immune response which is elicited by the selected polynucleotide. With regard to administering the expression vector *in vivo*, the specification only provides a prophetic working

example of using a mouse model for human cancer in which SCID mice are injected with human tumor cells stably transfected with reporter constructs in which the HSP70B promoter is driving the expression of TAT and in which the HIV-1 or HIV-2 promoter is driving either EGFP or IL-2 expression, growing the tumors to an appropriate size, heating the tumors using ultrasound, and measuring the level of expression of EGFP or IL2, or alternatively, injecting human tumor cells into SCID mice, growing the cells to an appropriate size, injecting the tumors DNA-lipid complexes, heating the tumors with ultrasound, and measuring gene expression. The efficacy of the treatments is indicated by a decrease in tumor size, decrease in metastatic activity, decrease in cell proliferation, or a halt in the tumor growth (see page 69, Example 4, of the specification). However, there are no working examples of the methods, nor are there any indications as to whether EGFP or IL2 expression will effect tumor size, metastatic activity, cell proliferation or growth of any and all tumors. In addition, there is no correlation between the *in vitro* results disclosed in the specification, and *in vivo* results of administering the expression constructs. In view of the insufficient guidance in the specification, and the lack of working examples, one of skill in the art would not have a high expectation of successfully utilizing the expression construct in the claim-designated methods to achieve the intended physiological response.

Moreover, at the time of filing, the art of gene therapy was known to unpredictable and non-routine. In the "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" (published December 7, 1995), Orkin and Motulsky indicate that clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol; that major difficulties of gene therapy include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host; that it is not always possible to extrapolate directly from animal experiments to human studies; and that while the most straight-forward application of gene therapy may be in the treatment of single-gene inherited disorders, practical difficulties need to be addressed, i.e. delivery of the appropriate gene to a specific cell type or tissue, gaining access to the relevant cell type for correction of the defect, assessing the total fraction of cells in a tissue that need to be corrected, achieving the level of

expression required for correction, and regulating expression of the added gene once it is transferred into appropriate target cells (see, e.g., pages 1 and 2, points 2, 3, and 5, for example, page 5, under "Single-gene inherited disorders", and page 14, bullet paragraphs 3-6). Similarly, Verma *et al.* (Nature, 387:239-242, 1997) indicate that "In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged; problems such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions remain formidable challenges; although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (see page 239, under Abstract, and left column, paragraphs 1-2). Note that the obstacles apply to the claim-designated viral vectors, i.e., retroviral, adenoviral, and adeno-associated viral vector delivery systems (see, e.g., pages 240 and 241, under the sections entitled "Retroviral vectors", "Adenoviral vectors", and "Adeno-associated viral vectors"). Furthermore, Ledley (Pharmaceutical Research, 13:1595-1614, 1996) discloses that while there is growing confidence that gene therapy will provide important pharmaceutical products, and that clinical trials have demonstrated that genes can be introduced into patients by several different methods and will express potentially therapeutic gene products, significant hurdles remain. Several recent clinical studies failed to demonstrate the expected pharmacological effects. Moreover, some of the methods that have been proposed for gene therapy have limiting toxicities, are difficult to manufacture and quality control, or are more costly than current therapies (see page 1595, right column, second paragraph). Retroviral vectors can be directly administered to patients, though the applicability of this approach is limited by the rapid inactivation of retroviruses by human complement (see page 1596, right column, last paragraph bridging page 1597). The major limitation of adeno-associated viruses has been difficulty in developing packaging cell lines that will produce sufficient titers of the virus for clinical use without the presence of helper virus (see, page 1597, right column, lines 1-4). Adenoviral vectors have been demonstrated to be toxic, inducing cytopathic and immunogenic responses *in vivo*. Preclinical and clinical studies have demonstrated that the level and persistence

of gene expression using adenoviral vectors may be inhibited by the immunological responses against the adenoviral particle, and inflammation in tissues targeted by the vector (see page 1597, right column, last paragraph). Moreover, Ledley states that the effectiveness of gene delivery *in vivo* is poorly predicted by *in vitro* results. Reasons why *in vitro* results would not be recapitulated *in vivo* include various biological barriers that are not reflected in *in vitro* models, and interactions between DNA or formulated DNA complexes with serum and blood elements (see page 1603, right column).

Treating cancer by utilizing gene therapy techniques is also unpredictable. For example, Gura (Science, 278:1041-1042, 1997) reports that in the xenograft model, i.e., a model in which animals carry transplanted human tumors, very few drugs tested that showed anticancer activity in xenografts made it into the clinic; that animals apparently do not handle the drugs exactly the way the human body does, and that attempts to use human cells in culture don't fare any better, partly because cell culture provides no information about whether a drug will make it to the tumor sites (page 1041, left company, 3rd paragraph). In addition, the xenograft tumors don't behave like naturally occurring tumors in humans, for example, by spreading to other tissues. In clonogenic assays, in which cell lines or patient's tumor cells are grown, *in vitro*, are monitored for the response to various anticancer treatments. However, the clonogenic assays can't always predict how a tumor will respond to a drug in an animal (see page 1042, left column, last paragraph through the right column, first paragraph). Genetically engineered mice to create better models of cancer development have also been developed. The mice are genetically altered to so that they carry the same kinds of changes, either abnormal activation of cancer-promoting oncogenes or loss of tumor-suppressor genes, that lead to cancer in humans, with the hope that the mice will develop tumors that behave the same way as do human tumors. However, the results of the genetically modified mouse model have been mixed. For example, in a mutant mouse which lacks a working APC gene, i.e., a tumor suppressor that leads to colon cancer when lost or inactivated, the mouse does well at recreating the early signs of colon cancer, but at later stages of the disease,

the type of mutations in the tumors diverge from those in human colon cancer, and the disease manifests itself differently as well. As another example, inactivation of the retinoblastoma tumor-suppressor gene in mice results in pituitary gland tumors, wherein in humans, inactivation results in cancer in the retina. As a last example, BRCA1 knock-out mice, which are intended to simulate human breast and ovarian cancer, do not get any tumors at all (see page 1041, right column, second paragraph, through page 1042, left column through the first full paragraph). Similarly, Gomez-Navarro *et al.* (European Journal of Cancer, 35:867-885, 1999) disclose the unpredictability of molecular chemotherapy as well as genetic immunopotentiation. With regard to molecular chemotherapy, Gomez-Navarro *et al.* indicate that "To date, the strategy of molecular chemotherapy has been mainly used in loco-regional disease models to overcome the lack of targeted vector systems. In these *in situ* schemes, a vector encoding the toxin gene is administered intratumorally or into an anatomic compartment containing the tumor mass. The goals of this delivery method are to achieve high local vector concentration in order to favor tumor transduction and to limit vector dissemination. However, transduction efficiencies of presently available vectors have been shown to be inadequate. Even in the context of closed compartment delivery, it has not been possible to modify a sufficient number of tumor cells to achieve a clinically relevant tumoral response".

With respect to immunotherapy, Leitner *et al.* (Vaccine, 18:765-777, 2000) disclose that "genetic vaccines can be delivered into the host by several routes and methods...Despite the large number of genetic vaccine studies conducted so far, many of the results are difficult to compare and inconsistent" (see page 766, right column, last paragraph). In addition, a variety of factors determine the immunogenicity of genetic vaccines such as the structure of the plasmid backbone, amount of plasmid delivered, expression levels of the antigen, immunization schedule, route of immunization, target-tissue, number of immunizations, presence or absence of introns in front of the gene, strain of the particular species, age of animals, and toxicity of the antigen for transfected host cells (see, e.g., page 767, Table 1). Inasmuch as one of skill in the art would not be able to

determine, a priori, whether administering a genetic vaccine will have the expected pharmaceutical effect, and in view of the lack of specific teachings in the specification with respect to the type of plasmid backbone, amount of plasmid delivered, expression levels of the antigen, immunization schedule, route of immunization, target-tissue, etc., the skilled artisan would not have had a high expectation of significantly enhancing the pharmacological effect produced by a peptide expressed in a patient by administering an expression vector comprising a polynucleotide encoding a peptide of interest without undue experimentation.

The claimed invention is also directed to the therapeutic application of antisense RNA and ribozymes. The instant specification does not disclose how to make the antisense RNA and ribozymes, nor does the specification provide any working examples that would show how one of skill in the art would apply these antisense RNAs and ribozymes in a therapy.

Branch (TIBS, 23:45-50, 1998) addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity; [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compound's primary pharmacological identity; [a]ntisense compounds are

no exception; [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites; [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*." Agrawal (TIBTECH, Vol. 14:376-387, 1996) states the following: "[t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (see page 376, left column, first paragraph); "[o]ligonucleotides must be taken up by cells in order to be effective; [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (see page 378, under "Cell culture system and target gene"); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (see page 379, left column, lines 4-7); "[a]ny antisense activity observed in such

artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (see page 379, left column, first full paragraphs).

With regard to altering the genetic material of a mammal (claim 38), the specification discloses that the expression construct can also optionally be used in a method of altering the genetic material of a mammal. There is no guidance as to what particular expression construct should be utilized, which cells should be altered, the mode of delivery for the cells to be altered, what the expected phenotype of such alteration would be and how one of skill in the art would use such a genetically altered mammal. Given the unpredictability of gene therapy as discussed above, and the lack of guidance in the specification as to how to reproducibly and predictably apply the claimed method to obtain a genetically altered mammal, one of skill in the art would not have a high expectation of producing the genetically altered mammal without undue experimentation, nor would one of skill in the art know how to use the genetically altered mammal produced by the method.

With regard to expression constructs comprising the inducible promoters, HSP28, HSP72 or HSP73, as discussed in the above written description rejection, the specification does not disclose the source of the promoters, nor does the specification disclose any sequence data associated with the heat shock promoters HSP28, HSP72 or HSP73. In addition, it is not apparent from the specification nor from a search of the prior art that hsp28, hsp72, and hsp73 promoters have been isolated and characterized. In view of the lack of guidance in the specification, and the absence of teachings in the prior art of heat shock inducible promoter sequences obtained from hsp28, hsp72, or hsp73 genes, the skilled artisan would not have a high expectation of making or using expression constructs comprising these promoters without undue experimentation.

In view of the of the unpredictability of the effectiveness of gene therapy and immunotherapy, the lack of guidance in the specification of how to make and use the therapeutic agents for gene therapy and immunotherapy, and the limited showings in the specification, one of

skill in the art would not have had a high expectation of successfully making and using the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 38, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 41 are rendered vague and indefinite by the recitation of "HSP 28", "HSP72" and "HSP73" promoters as it is unclear what nucleic sequences are encompassed in these promoters as the promoter sequences are not defined in the specification nor in the prior art.

Claim 38 is rendered vague and indefinite by the phrase "said selected polynucleotide" on line 5 as there is no previous recitation of a selected polynucleotide. The phrase lacks antecedent basis. The term "said" should be changed to "a" to overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-7, 9, 10-12, 14, 16, 39-41, 43, 44, and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Bromley *et al.* (EP 0299127, 1989).

Bromley *et al.* disclose modified inducible hybrid genes, i.e., expression constructs, comprising 1) genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a heat shock promoter (see page 3, lines 51-58, and page 4, lines 1-5), such as the hsp70 promoter (see, e.g., pages 5 and 6, under "Plasmid constructions). The constructs can be introduced into host cells in the form of plasmid vectors and the constructs and vectors can comprise either one or both of the genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a human heat shock promoter, and can further comprise a selectable marker (see, e.g., page 4, lines 1-3, and lines 22-31, page 5, lines 1-3, and claims 1, 9, and 10). The hybrid genes can be part of one or separate vectors whereby incorporation into host cells is carried out by transfection or co-transection (see page 4, lines 28-29). The gene of interest includes viral antigens, blood factors, hormones, enzymatically active proteins, structural proteins, proteins for diagnostic tests, e.g., TNF and interleukin, and other products of clinical and pharmaceutical interest (see page 4, lines 17-21). The inducible hsp promoter is activated by hyperthermic conditions. Transfection of the cells with the expression construct comprising the hybrid genes, and exposure to heat treatment at 42.5°C or 43°C (which can be considered about 40°C or 41°C or 42°C), result in expression of the hybrid constructs (see, e.g., page 6, lines 24-29, and Tables 1-3).

Thus, the disclosure of Bromley *et al.* anticipates the claimed invention.

Claims 1, 10, 12, 13, 15, 16, 39, and 44-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Gage *et al.* (U.S. Patent No. 5,770,414, 1998, effective filing date of 2/20/96).

Gage *et al.* disclose an expression construct comprising 1) an inducible promoter operably linked to a gene encoding a transactivating factor, 2) a second promoter operably linked to the selected polynucleotide which is a protein, wherein the second promoter is activated by the

transactivating factor, 3) a gene encoding a selectable marker, 4) and an internal ribosome entry site positioned between a first and second selected polynucleotide (see, e.g., column 4, lines 21-65, column 5, lines 17-48, and Figure 1). Gage *et al.* further disclose introducing the expression construct into neuronal progenitor cells, *in vitro*, wherein the introduction of the expression construct is mediated by a retroviral vector, to obtain expression of the selected polynucleotides (column 6, lines 29-41, Examples 3 and 4).

Thus, the disclosure of Gage *et al.* anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 7, and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bromley *et al.* (EP 0299127, 1989), taken with any one of Stover (U.S. Patent No. 5,583,038, 1996, filed 1992), Hickey *et al.* (Nucleic Acids Research, 14:4127-4145, 1986), Gaestel *et al.* (Gene, 128:279-283, 1993), Dale *et al.* (Gene, 172:279-284, 1996), or Quail *et al.* (EP 0342926, 1989).

Bromley *et al.* disclose modified inducible hybrid genes, i.e., expression constructs, comprising 1) genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a heat shock promoter (see page 3, lines 51-58, and page 4, lines 1-5), such as the hsp70 promoter (see, e.g., pages 5 and 6, under "Plasmid constructions). The constructs can be introduced into host cells in the form of plasmid vectors and the constructs and vectors can comprise either one or both of the genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a human heat shock promoter, and can further comprise a selectable marker (see, e.g., page 4, lines 1-3, and lines 22-31, page 5, lines 1-3, and claims 1, 9, and 10). The hybrid genes can be part of one or separate vectors whereby incorporation into host cells is carried out by transfection or co-transection (see page 4, lines 28-29). The gene of interest includes viral antigens, blood factors, hormones, enzymatically active proteins, structural proteins, proteins for diagnostic tests, e.g., TNF and interleukin, and other products of clinical and pharmaceutical interest (see page 4, lines 17-21). The inducible hsp promoter is activated by hyperthermic conditions. Transfection of the cells with the expression construct comprising the hybrid genes, and exposure to heat treatment at 42.5°C or 43°C (which can be considered about 40°C or 41°C or 42°C), result in expression of the hybrid constructs (see, e.g., page 6, lines 24-29, and Tables 1-3). Bromley *et al.* disclose that the advantage of this inducible expression construct is that a substantially prolonged time of expression is observed upon a single heat activation cycle whereas in non-hybrid inducible expression constructs, multiple cycles of heat activation are required for continued expression of the construct which is technically inconvenient when producing large quantities of the gene of interest, and may result in cell growth inhibition and subsequent cell death (see page 2, lines 34-39, and page 3, lines 6-23).

Bromley *et al.* do not disclose all of the claim-designated inducible promoters. However, Stover discloses expression vectors comprising the hsp60 or hsp70 promoter operably linked to a gene of interest (see, e.g., column 3, lines 41-53). Alternatively, Hickey *et al.* disclose an expression construct comprising the human hsp27 promoter fragment operably linked to a polynucleotide encoding a gene of interest which is induced by heat shock (see, e.g., pages 4135

and 4137, under "Expression of the cloned genes in vitro and in vivo"). Alternatively, Gaestel *et al.* disclose hsp25 and hsp27 promoter fragments which contain similar transcriptional regulatory elements including the putative heat shock element consensus sequence (see, e.g., pages 282-283, under "Comparison of the mouse hsp25 and human hsp27", and Figure 4). Alternatively, Dale *et al.* disclose an expression construct comprising the murine 84 kDa heat shock protein promoter, which is one of two genes which code for hsp90 proteins, operatively linked to a gene of interest, and which is induced by heat shock (see, e.g., page 279 under "Summary", and pages 281-282, under "Characterization of the HS response and the HSE", and Figure 3). Alternatively, Quail *et al.* disclose an expression construct comprising a ubiquitin promoter system, operably linked to a gene of interest, and which is induced by heat shock (see, e.g., page 11, Examples 2 and 3). Quail *et al.* also disclose that the disclosed ubiquitin promoter is similar to the ubiquitin promoter of chicken embryo fibroblasts, and further teach that ubiquitin promoters have been shown to up-regulate expression of ubiquitin in response to heat shock in yeast, chicken embryo fibroblasts and maize (see, e.g., page 12, Example 4).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the expression construct of Bromley *et al.* by substituting the hsp70 promoter of Bromley *et al.* with the hsp60 promoter disclosed by Stover, or the hsp27 promoter disclosed by Hickey *et al.*, or the hsp25 or hsp27 promoters disclosed by Gaestel *et al.*, or the hsp90 promoter disclosed by Dale *et al.*, or the ubiquitin promoter disclosed by Quail *et al.* in view of the teachings of Bromley *et al.* that the hsp70 promoter can be substituted with hsp promoters obtained from hsp proteins of different molecular weights, or with other inducible promoters. As modifying portions of expression constructs, including promoters and regulatory elements, is well known in the art of molecular biology, one of ordinary skill in the art would have had a high expectation of successfully modifying the expression construct of Bromley *et al.* to include any one of the known inducible promoters, as taught by Stover, Hickey *et al.*, Gaestel *et al.*, Dale *et al.*, or Quail *et al.* in the generation of an expression construct, for the purpose of providing a construct which can

be suitably regulated by environmental conditions as clearly disclosed by Bromley *et al.* without undue experimentation, barring evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 1, 8, 39, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bromley *et al.* (EP 0299127, 1989), taken with either Webster *et al.* (U.S. Patent No. 5,834,306, 1998, effective filing date of 12/23/94) or Dachs *et al.* (Nature Medicine, 3:515-520, 1997).

Bromley *et al.* disclose modified inducible hybrid genes, i.e., expression constructs, comprising 1) genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a heat shock promoter (see page 3, lines 51-58, and page 4, lines 1-5), such as the hsp70 promoter (see, e.g., pages 5 and 6, under "Plasmid constructions). The constructs can be introduced into host cells in the form of plasmid vectors and the constructs and vectors can comprise either one or both of the genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a human heat shock promoter, and can further comprise a selectable marker (see, e.g., page 4, lines 1-3, and lines 22-31, page 5, lines 1-3, and claims 1, 9, and 10). The hybrid genes can be part of one or separate vectors whereby incorporation into host cells is carried out by transfection or co-transection (see page 4, lines 28-29). The gene of interest includes viral antigens, blood factors, hormones, enzymatically active proteins, structural proteins, proteins for diagnostic tests, e.g., TNF and interleukin, and other products of clinical and pharmaceutical interest (see page 4, lines 17-21). The inducible hsp promoter is activated by hyperthermic conditions. Transfection of the cells with the expression construct comprising the hybrid genes, and exposure to heat treatment at 42.5°C or 43°C (which can be considered about 40°C or 41°C or 42°C), result in expression of the hybrid constructs (see, e.g., page 6, lines 24-29, and Tables 1-3). Bromley *et al.* disclose that the advantage of this inducible expression construct is that a substantially prolonged time of expression is observed

upon a single heat activation cycle whereas in non-hybrid inducible expression constructs, multiple cycles of heat activation are required for continued expression of the construct which is technically inconvenient when producing large quantities of the gene of interest, and may result in cell growth inhibition and subsequent cell death (see page 2, lines 34-39, and page 3, lines 6-23).

Bromley *et al.* do not disclose that the inducible promoter comprises a hypoxia-responsive element. However, Webster *et al.* disclose a chimeric gene containing a hypoxia response element, a therapeutic gene, and a tissue-specific promoter operably linked to the therapeutic gene to control transcription of the therapeutic gene in the cell, where the element is effective to modulate expression of the therapeutic gene. Exposing the cell to hypoxic conditions enhances expression of the gene (see, e.g., column 4, lines 19-27, column 11, line 26 through column 12, line 14). Alternatively, Dachs *et al.* disclose an expression construct comprising a hypoxia response element from the mouse PGK-1 enhancer which is used to drive expression of a heterologous gene within the mass of a solid tumor. And disclose combining the hypoxia responsive element with different promoters to achieve hypoxia-inducible expression from different basal levels (see, e.g., page 515, right column, under "Hypoxia induces marker gene expression in vitro", page 516, Figure 2, and page 517, right column, under "Discussion"). Dachs *et al.* disclose the utility of using different promoters and different heterologous gene products as a tool for potential diagnostic approaches to tumor hypoxia (see page 518, left column).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the expression construct of Bromley *et al.* by modifying the inducible promoter to include a hypoxia responsive element as disclosed by Webster *et al.* or Dachs *et al.*, in view of the teachings of either Webster *et al.* or Dachs *et al.* that this element effectively modulates gene expression under hypoxic conditions. As modifying portions of expression constructs, including promoters and regulatory elements, is well known in the art of molecular biology, one of ordinary skill in the art would have had a high expectation of successfully modifying the expression construct of Bromley *et al.* by including an additional regulatory element, such as the hypoxia-responsive element of Webster *et al.* or Dachs *et al.*, to produce an expression construct, for the purpose of

providing a construct, which can be regulated by a variety of environmental/physiological conditions, without undue experimentation, barring evidence to the contrary. One of ordinary skill in the art would have been motivated to generate such an expression construct which can be regulated by different environmental factors, such as hyperthermic and hypoxic conditions as a research tool to determine, for example, diagnostic approaches to tumor hypoxia.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 1, 10, 11, 39, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bromley *et al.* (EP 0299127, 1989), taken with any one of Dubensky, Jr. *et al.* (U.S. Patent No. 5,814,482, 1998, effective filing date of 9/14/94), Scott *et al.* (WO 95/09913, 1995), Saito *et al.* (U.S. Patent No. 5,817,492, 1998, effective filing date of 8/30/95), Weinberg *et al.* (WO 89/10412, 1989), Beach *et al.* (5,889,169, 1999, effective filing date of 5/25/94), or Tewari *et al.* (Biochim. Biophys. Acta, 1209:293-295, 1994).

Bromley *et al.* disclose modified inducible hybrid genes, i.e., expression constructs, comprising 1) genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a heat shock promoter (see page 3, lines 51-58, and page 4, lines 1-5), such as the hsp70 promoter (see, e.g., pages 5 and 6, under "Plasmid constructions). The constructs can be introduced into host cells in the form of plasmid vectors and the constructs and vectors can comprise either one or both of the genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a human heat shock promoter, and can further comprise a selectable marker (see, e.g., page 4, lines 1-3, and lines 22-31, page 5, lines 1-3, and claims 1, 9, and 10). The hybrid genes can be part of one or separate vectors whereby incorporation into host cells is carried out by transfection or co-transection (see page 4, lines 28-29). The gene of interest includes viral antigens, blood factors, hormones, enzymatically active proteins, structural proteins, proteins for diagnostic tests, e.g., TNF and interleukin, and other

products of clinical and pharmaceutical interest (see page 4, lines 17-21). The inducible hsp promoter is activated by hyperthermic conditions. Transfection of the cells with the expression construct comprising the hybrid genes, and exposure to heat treatment at 42.5°C or 43°C (which can be considered about 40°C or 41°C or 42°C), result in expression of the hybrid constructs (see, e.g., page 6, lines 24-29, and Tables 1-3). Bromley *et al.* disclose that the advantage of this inducible expression construct is that a substantially prolonged time of expression is observed upon a single heat activation cycle whereas in non-hybrid inducible expression constructs, multiple cycles of heat activation are required for continued expression of the construct which is technically inconvenient when producing large quantities of the gene of interest, and may result in cell growth inhibition and subsequent cell death (see page 2, lines 34-39, and page 3, lines 6-23).

Bromley *et al.* do not disclose all of the claim-designated selected polynucleotides encoding various proteins of interest. However, Dubensky, Jr. *et al.* disclose a vector system for expressing a polynucleotide of interest wherein the polynucleotide of interest can encode a protein selected from IL-1, IL-2, IL-4, IL-7, IL-12, IL-15, IFN alpha or gamma, G-CSF, GM-CSF, TNF, ICAM-1, Flt-3 ligand, HSV-tk, antisense polynucleotides including antisense thymidine kinase, antisense dihydrofolate reductase, antisense HER2, antisense ABL, and antisense Myc, and ribozymes (see, e.g., column 4, lines 29-38, column 20 line 39 through column 21, line 22, column 22, line 63 through column 23, line 8, and lines 25-38, column 34, lines 41-65, column 42, lines 4-17). Alternatively, Scott *et al.* disclose nucleotide sequences encoding TIMP-3 which may be used to produce purified TIMP-3 using well-known methods of recombinant DNA technology. Scott *et al.* indicate that the advantages of producing the TIMP-3 by recombinant DNA technology include obtaining highly enriched sources of the proteins for purification and the availability of simplified purification procedures (see, e.g., page 17, first full paragraph, and pages 25-27, under "Expression of cDNA clones"). Alternatively, Saito *et al.* disclose a vector system for expressing a polynucleotide of interest wherein the polynucleotide of interest can encode a protein selected from the interleukins, interferons, tumor necrosis factor, granulocyte colony stimulating factor, macrophage colony stimulating factor, HLA-B7, antioncogenes such as p53,

antisense sequences and suicide genes (see, e.g., column 7, lines 14-31). Alternatively, Weinberg *et al.* disclose a vector system for expressing a polynucleotide of interest wherein the polynucleotide of interest encodes the neu protein (see, e.g., page 49, lines 10-27, and Figure 8). Alternatively, Beach *et al.* disclose a vector system for expressing a polynucleotide of interest wherein the polynucleotide of interest encodes p16 (see, e.g., column 25, lines 21-61). Alternatively, Tewari *et al.* disclose a polynucleotide encoding the human ornithine decarboxylase antizyme protein (see, e.g., pages 293-295).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the expression construct of Bromley *et al.* by substituting one polynucleotide encoding a protein of interest with another polynucleotide encoding a protein of interest, such as those disclosed by Dubensky, Jr. *et al.*, the polynucleotide encoding TIMP-3, as disclosed by Scott *et al.*, or any of the polynucleotides disclosed by Saito *et al.*, such as HLA-B7 or p53, the neu polynucleotide disclosed by Weinberg *et al.*, or the p16 polynucleotide disclosed by Beach *et al.*, or the ornithine decarboxylase antizyme polynucleotide disclosed by Tewari *et al.* in view of the teachings of Bromley *et al.* that different numerous genes of interest and products of clinical and pharmaceutical interest can be readily incorporated into the expression construct. As substituting one polynucleotide encoding a peptide for another in an expression system is well known in the art of molecular biology, one of ordinary skill in the art would have had a high expectation of successfully substituting the genes of interest disclosed by Bromley *et al.* with the genes of interest disclosed by Dubensky, Jr. *et al.*, Scott *et al.*, Saito *et al.*, Weinberg *et al.*, Beach *et al.*, or Tewari *et al.* to produce a recombinant protein of interest without undue experimentation barring evidence to the contrary. Moreover, one of skill in the art would have been motivated to use the expression construct of Bromley *et al.* for producing large quantities of protein in view of the advantages disclosed by Bromley *et al.* in using such an expression construct.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 1, 9, 39, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bromley *et al.* (EP 0299127, 1989), taken with Emerman *et al.* (Embo J. 6:3755-3760, 1987).

Bromley *et al.* disclose modified inducible hybrid genes, i.e., expression constructs, comprising 1) genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a heat shock promoter (see page 3, lines 51-58, and page 4, lines 1-5), such as the hsp70 promoter (see, e.g., pages 5 and 6, under "Plasmid constructions). The constructs can be introduced into host cells in the form of plasmid vectors and the constructs and vectors can comprise either one or both of the genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a human heat shock promoter, and can further comprise a selectable marker (see, e.g., page 4, lines 1-3, and lines 22-31, page 5, lines 1-3, and claims 1, 9, and 10). The hybrid genes can be part of one or separate vectors whereby incorporation into host cells is carried out by transfection or co-transection (see page 4, lines 28-29). The gene of interest includes viral antigens, blood factors, hormones, enzymatically active proteins, structural proteins, proteins for diagnostic tests, e.g., TNF and interleukin, and other products of clinical and pharmaceutical interest (see page 4, lines 17-21). The inducible hsp promoter is activated by hyperthermic conditions. Transfection of the cells with the expression construct comprising the hybrid genes, and exposure to heat treatment at 42.5°C or 43°C (which can be considered about 40°C or 41°C or 42°C), result in expression of the hybrid constructs (see, e.g., page 6, lines 24-29, and Tables 1-3). Bromley *et al.* disclose that the advantage of this inducible expression construct is that a substantially prolonged time of expression is observed upon a single heat activation cycle whereas in non-hybrid inducible expression constructs, multiple cycles of heat activation are required for continued expression of the construct which is technically inconvenient when producing large quantities of the gene of interest, and may result in cell growth inhibition and subsequent cell death (see page 2, lines 34-39, and page 3, lines 6-23).

Bromley *et al.* do not disclose an expression construct comprising either the HIV-1 or the HIV-2 promoter. However, Emerman *et al.* disclose that the both HIV-1 and the HIV-2

promoters can be used to direct expression of a polynucleotide encoding a protein of interest in the presence of tat (see, e.g., page 3755, under Introduction, and Figure 1).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the expression construct of Bromley *et al.* by substituting the HIV-1 promoter operably linked to a selected polynucleotide with the HIV-2 promoter operably linked to a selected polynucleotide in view of the teachings of Emerman *et al.*, that both the HIV-1 and the HIV-2 promoters are regulated by the transactivating factor tat, and further in view of the teachings of Bromley *et al.* that different promoters can be successfully used as inducible promoters in the expression construct. As substituting one promoter for another in an expression system is well known in the art of molecular biology, one of ordinary skill in the art would have had a high expectation of successfully substituting one promoter for another to generate an expression construct which is inducible under appropriate conditions, to produce the recombinant protein of interest without undue experimentation barring evidence to the contrary. Moreover, one of skill in the art would have been motivated to use the expression construct of Bromley *et al.* for producing large quantities of protein in view of the advantages disclosed by Bromley *et al.* in using such an expression construct.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bromley *et al.* (EP 0299127, 1989), taken with either of Loeb *et al.* (U.S. Patent No. 5,877,010, 1999, effective filing date of 5/2/95), Hancock (in Methods in Molecular Biology, 8, Practical Molecular Virology, Viral Vectors for Gene Expression, ed. M. Collins, Humana Press Inc., Clifton, New Jersey, 1991, Chapter 14, pages 164-165) or Talavera *et al.* (in Methods in Molecular Biology, 8, Practical Molecular Virology, Viral Vectors for Gene Expression, ed. M. Collins, Humana Press Inc., Clifton, New Jersey, 1991, Chapter 21, pages 235-248).

Bromley *et al.* disclose modified inducible hybrid genes, i.e., expression constructs, comprising 1) genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a heat shock promoter (see page 3, lines 51-58, and page 4, lines 1-5), such as the hsp70 promoter (see, e.g., pages 5 and 6, under "Plasmid constructions). The constructs can be introduced into host cells in the form of plasmid vectors and the constructs and vectors can comprise either one or both of the genes of interest operably linked to HIV LTR promoter sequences and 2) a tat-III gene operably linked to a human heat shock promoter, and can further comprise a selectable marker (see, e.g., page 4, lines 1-3, and lines 22-31, page 5, lines 1-3, and claims 1, 9, and 10). The hybrid genes can be part of one or separate vectors whereby incorporation into host cells is carried out by transfection or co-transection (see page 4, lines 28-29). The gene of interest includes viral antigens, blood factors, hormones, enzymatically active proteins, structural proteins, proteins for diagnostic tests, e.g., TNF and interleukin, and other products of clinical and pharmaceutical interest (see page 4, lines 17-21). The inducible hsp promoter is activated by hyperthermic conditions. Transfection of the cells with the expression construct comprising the hybrid genes, and exposure to heat treatment at 42.5°C or 43°C (which can be considered about 40°C or 41°C or 42°C), result in expression of the hybrid constructs (see, e.g., page 6, lines 24-29, and Tables 1-3). Bromley *et al.* disclose that the advantage of this inducible expression construct is that a substantially prolonged time of expression is observed upon a single heat activation cycle whereas in non-hybrid inducible expression constructs, multiple cycles of heat activation are required for continued expression of the construct which is technically inconvenient when producing large quantities of the gene of interest, and may result in cell growth inhibition and subsequent cell death (see page 2, lines 34-39, and page 3, lines 6-23).

Bromley *et al.* do not disclose all of the claim-designated delivery vehicles for introducing the expression vector into a cell. However, Loeb *et al.* disclose expression constructs which can be introduced into cells using viral vectors such as herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors, pox vectors, parvoviral vectors, baculovirus vectors, and retroviral vectors (see, e.g., column 3, line 59 through column 4, line 4). Note that retroviral

vectors encompass lentiviral vectors. Alternatively, Hancock discloses introducing expression constructs into cells using liposomes (see e.g., pages 164-165, under "Transfection of Cells in Culture"). Alternatively, Talavera *et al.* disclose introducing expression constructs into cells using vaccinia viruses (see, e.g., pages 235-248).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the method of Bromley *et al.* of introducing an expression construct into a cell by utilizing any of the well known gene transfer methodologies established in the art of molecular biology. Thus, utilizing the gene transfer systems such as herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors, pox vectors, parvoviral vectors, baculovirus vectors, and retroviral vectors disclosed by Loeb *et al.*, or the liposome-based delivery system disclosed by Hancock, or the vaccinia virus-based delivery system of Talavera *et al.*, would have been obvious and well within the purview of one of ordinary skill in the art of molecular biology. Moreover, as these delivery methods are well-established in the art, the artisan of ordinary skill would have had a high expectation of successfully introducing an expression construct into a cell, *in vitro*, utilizing any of the well-known gene transfer delivery systems, barring evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirement of 37 CFR 1.821(d) as reference must be made to the sequence disclosed in Figure 10, either in the figure or in the text of the description of the figure, by use of the sequence identifier, preceded by "SEQ ID NO:".

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633.

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